

1 PRESCRIBING INFORMATION

2 **FLOVENT<sup>®</sup> DISKUS<sup>®</sup> 50 mcg**  
3 **(fluticasone propionate inhalation powder, 50 mcg)**

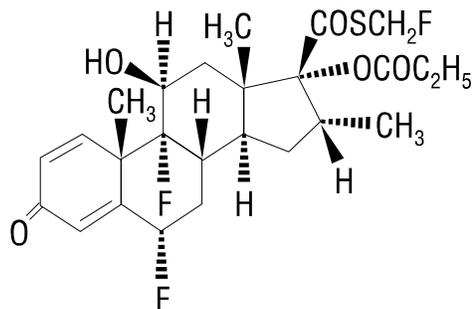
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5 **FLOVENT<sup>®</sup> DISKUS<sup>®</sup> 100 mcg**  
6 **(fluticasone propionate inhalation powder, 100 mcg)**

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8 **FLOVENT<sup>®</sup> DISKUS<sup>®</sup> 250 mcg**  
9 **(fluticasone propionate inhalation powder, 250 mcg)**

10  
11 **For Oral Inhalation Only**

12 **DESCRIPTION**

13 The active component of FLOVENT DISKUS 50 mcg, FLOVENT DISKUS 100 mcg, and  
14 FLOVENT DISKUS 250 mcg is fluticasone propionate, a corticosteroid having the chemical  
15 name *S*-(fluoromethyl) 6 $\alpha$ ,9-difluoro-11 $\beta$ ,17-dihydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-  
16 17 $\beta$ -carbothioate, 17-propionate and the following chemical structure:



18  
19  
20 Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and  
21 the empirical formula is C<sub>25</sub>H<sub>31</sub>F<sub>3</sub>O<sub>5</sub>S. It is practically insoluble in water, freely soluble in  
22 dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

23 FLOVENT DISKUS 50 mcg, FLOVENT DISKUS 100 mcg, and FLOVENT DISKUS  
24 250 mcg are specially designed plastic inhalation delivery systems containing a double-foil  
25 blister strip of a powder formulation of fluticasone propionate intended for oral inhalation only.  
26 The DISKUS<sup>®</sup> inhalation unit, which is the delivery component, is an integral part of the drug  
27 product. Each blister on the double-foil strip within the unit contains 50, 100, or 250 mcg of  
28 microfine fluticasone propionate in 12.5 mg of formulation containing lactose (which contains  
29 milk proteins). After a blister containing medication is opened by activating the DISKUS, the  
30 medication is dispersed into the airstream created by the patient inhaling through the  
31 mouthpiece.

32 Under standardized in vitro test conditions, FLOVENT DISKUS delivers 46, 94, or 235 mcg  
33 of fluticasone propionate from FLOVENT DISKUS 50 mcg, FLOVENT DISKUS 100 mcg, or  
34 FLOVENT DISKUS 250 mcg, respectively, when tested at a flow rate of 60 L/min for  
35 2 seconds. In adult patients with obstructive lung disease and severely compromised lung  
36 function (mean forced expiratory volume in 1 second [FEV<sub>1</sub>] 20% to 30% of predicted), mean  
37 peak inspiratory flow (PIF) through a DISKUS<sup>®</sup> was 82.4 L/min (range, 46.1 to 115.3 L/min). In  
38 children with asthma 4 and 8 years old, mean PIF through FLOVENT DISKUS was 70 and  
39 104 L/min, respectively (range, 48 to 123 L/min).

40 The actual amount of drug delivered to the lung may depend on patient factors, such as  
41 inspiratory flow profile.

## 42 **CLINICAL PHARMACOLOGY**

43 **Mechanism of Action:** Fluticasone propionate is a synthetic trifluorinated corticosteroid with  
44 potent anti-inflammatory activity. In vitro assays using human lung cytosol preparations have  
45 established fluticasone propionate as a human corticosteroid receptor agonist with an affinity 18  
46 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate  
47 (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of  
48 budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these  
49 results. The clinical significance of these findings is unknown.

50 Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have  
51 been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes,  
52 macrophages, and neutrophils) and mediator production or secretion (e.g., histamine,  
53 eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These  
54 anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

55 Though effective for the treatment of asthma, corticosteroids do not affect asthma symptoms  
56 immediately. Individual patients will experience a variable time to onset and degree of symptom  
57 relief. Maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment.  
58 When corticosteroids are discontinued, asthma stability may persist for several days or longer.

59 Studies in patients with asthma have shown a favorable ratio between topical  
60 anti-inflammatory activity and systemic corticosteroid effects with recommended doses of orally  
61 inhaled fluticasone propionate. This is explained by a combination of a relatively high local  
62 anti-inflammatory effect, negligible oral systemic bioavailability (<1%), and the minimal  
63 pharmacological activity of the only metabolite detected in man.

64 **Pharmacokinetics: Absorption:** Fluticasone propionate acts locally in the lung; therefore,  
65 plasma levels do not predict therapeutic effect. Studies using oral dosing of labeled and  
66 unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate  
67 is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the  
68 gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is  
69 systemically absorbed. The systemic bioavailability of fluticasone propionate from the DISKUS  
70 device in healthy volunteers averages 18%.

71 Peak steady-state fluticasone propionate plasma concentrations in adult patients with asthma  
72 (N = 11) ranged from undetectable to 266 pg/mL after a 500-mcg twice-daily dose of fluticasone  
73 propionate inhalation powder using the DISKUS device. The mean fluticasone propionate  
74 plasma concentration was 110 pg/mL.

75 **Distribution:** Following intravenous administration, the initial disposition phase for  
76 fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding.  
77 The volume of distribution averaged 4.2 L/kg.

78 The percentage of fluticasone propionate bound to human plasma proteins averages 91%.  
79 Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly  
80 bound to human transcortin.

81 **Metabolism:** The total clearance of fluticasone propionate is high (average, 1,093 mL/min),  
82 with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite  
83 detected in man is the 17 $\beta$ -carboxylic acid derivative of fluticasone propionate, which is formed  
84 through the cytochrome P450 3A4 pathway. This metabolite had less affinity (approximately  
85 1/2,000) than the parent drug for the corticosteroid receptor of human lung cytosol in vitro and  
86 negligible pharmacological activity in animal studies. Other metabolites detected in vitro using  
87 cultured human hepatoma cells have not been detected in man.

88 **Elimination:** Following intravenous dosing, fluticasone propionate showed polyexponential  
89 kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a  
90 radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in  
91 the feces as parent drug and metabolites.

92 **Special Populations: Hepatic Impairment:** Since fluticasone propionate is  
93 predominantly cleared by hepatic metabolism, impairment of liver function may lead to  
94 accumulation of fluticasone propionate in plasma. Therefore, patients with hepatic disease  
95 should be closely monitored.

96 **Gender:** Full pharmacokinetic profiles were obtained from 9 female and 16 male patients  
97 given 500 mcg twice daily. No overall differences in fluticasone propionate pharmacokinetics  
98 were observed.

99 **Pediatrics:** In a clinical study conducted in patients 4 to 11 years of age with mild to  
100 moderate asthma, fluticasone propionate concentrations were obtained in 61 patients at 20 and  
101 40 minutes after dosing with 50 and 100 mcg twice daily of fluticasone propionate inhalation  
102 powder using the DISKUS. Plasma concentrations were low and ranged from undetectable  
103 (about 80% of the plasma samples) to 88 pg/mL. Mean peak fluticasone propionate plasma  
104 concentrations at the 50- and 100-mcg dose levels were 5 and 8 pg/mL, respectively.

105 **Other:** Formal pharmacokinetic studies using fluticasone propionate have not been  
106 conducted in other special populations.

107 **Drug Interactions:** Fluticasone propionate is a substrate of cytochrome P450 3A4.  
108 Coadministration of fluticasone propionate and the highly potent cytochrome P450 3A4 inhibitor  
109 ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18  
110 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was

111 coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate  
112 concentrations following fluticasone propionate aqueous nasal spray alone were undetectable  
113 (<10 pg/mL) in most subjects, and when concentrations were detectable, peak levels ( $C_{max}$ )  
114 averaged 11.9 pg/mL (range, 10.8 to 14.1 pg/mL) and  $AUC_{(0-\tau)}$  averaged 8.43 pg•hr/mL (range,  
115 4.2 to 18.8 pg•hr/mL). Fluticasone propionate  $C_{max}$  and  $AUC_{(0-\tau)}$  increased to 318 pg/mL (range,  
116 110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range, 1,207.1 to 5,662.0 pg•hr/mL), respectively,  
117 after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This  
118 significant increase in plasma fluticasone propionate concentration resulted in a significant  
119 decrease (86%) in plasma cortisol area under the plasma concentration versus time curve (AUC).

120 Caution should be exercised when other potent cytochrome P450 3A4 inhibitors are  
121 coadministered with fluticasone propionate. In a drug interaction study, coadministration of  
122 orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted  
123 in increased plasma fluticasone propionate concentration and reduced plasma cortisol AUC, but  
124 had no effect on urinary excretion of cortisol.

125 In another multiple-dose drug interaction study, coadministration of orally inhaled fluticasone  
126 propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect  
127 fluticasone propionate pharmacokinetics.

128 **Pharmacodynamics:** In clinical trials with fluticasone propionate inhalation powder using  
129 doses up to and including 250 mcg twice daily, occasional abnormal short cosyntropin tests  
130 (peak serum cortisol <18 mcg/dL assessed by radioimmunoassay) were noted both in patients  
131 receiving fluticasone propionate and in patients receiving placebo. The incidence of abnormal  
132 tests at 500 mcg twice daily was greater than placebo. In a 2-year study carried out with the  
133 DISKHALER<sup>®</sup> inhalation device in 64 patients with mild, persistent asthma (mean FEV<sub>1</sub> 91% of  
134 predicted) randomized to fluticasone propionate 500 mcg twice daily or placebo, no patient  
135 receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin infusion (peak  
136 serum cortisol <18 mcg/dL). With a peak cortisol threshold <35 mcg/dL, 1 patient receiving  
137 fluticasone propionate (4%) had an abnormal response at 1 year; repeat testing at 18 months and  
138 2 years was normal. Another patient receiving fluticasone propionate (5%) had an abnormal  
139 response at 2 years. No patient on placebo had an abnormal response at 1 or 2 years.

140 In a placebo-controlled clinical study conducted in patients 4 to 11 years of age, a 30-minute  
141 cosyntropin stimulation test was performed in 41 patients after 12 weeks of dosing with 50 or  
142 100 mcg twice daily of fluticasone propionate via the DISKUS device. One patient receiving  
143 fluticasone propionate via DISKUS had a prestimulation plasma cortisol concentration  
144 <5 mcg/dL, and 2 patients had a rise in cortisol of <7 mcg/dL. However, all poststimulation  
145 values were >18 mcg/dL.

146 The potential systemic effects of inhaled fluticasone propionate on the  
147 hypothalamic-pituitary-adrenal (HPA) axis were also studied in patients with asthma.  
148 Fluticasone propionate given by inhalation aerosol at dosages of 220, 440, 660, or 880 mcg  
149 twice daily was compared with placebo or oral prednisone 10 mg given once daily for 4 weeks.  
150 For most patients, the ability to increase cortisol production in response to stress, as assessed by

151 6-hour cosyntropin stimulation, remained intact with inhaled fluticasone propionate treatment.  
152 No patient had an abnormal response (peak serum cortisol <18 mcg/dL) after dosing with  
153 placebo or fluticasone propionate 220 mcg twice daily. For patients treated with 440, 660, and  
154 880 mcg twice daily, 10%, 16%, and 12%, respectively, had an abnormal response as compared  
155 to 29% of patients treated with prednisone.

156 To confirm that systemic absorption does not play a role in the clinical response to inhaled  
157 fluticasone propionate, a double-blind clinical study comparing inhaled fluticasone propionate  
158 powder and oral fluticasone propionate was conducted. Inhaled fluticasone propionate powder in  
159 dosages of 100 and 500 mcg twice daily was compared to oral fluticasone propionate  
160 20,000 mcg once daily and placebo for 6 weeks. Plasma levels of fluticasone propionate were  
161 detectable in all 3 active groups, but the mean values were highest in the oral group. Both doses  
162 of inhaled fluticasone propionate were effective in maintaining asthma stability and improving  
163 lung function, while oral fluticasone propionate and placebo were ineffective. This demonstrates  
164 that the clinical effectiveness of inhaled fluticasone propionate is due to its direct local effect and  
165 not to an indirect effect through systemic absorption.

## 166 **CLINICAL TRIALS**

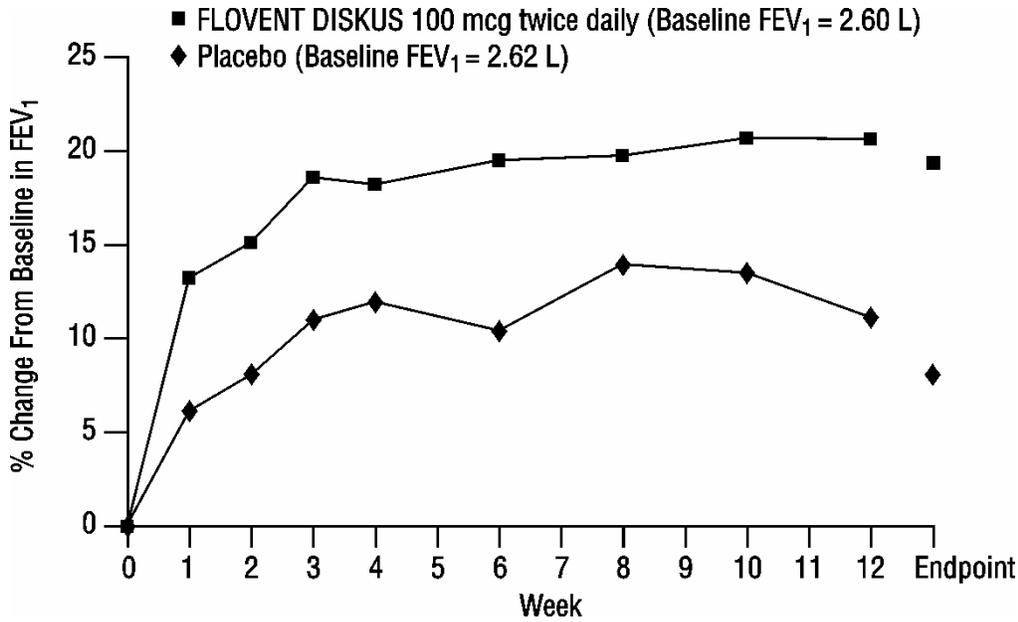
167 **Adult and Adolescent Patients 12 Years of Age and Older:** Four randomized,  
168 double-blind, parallel-group, placebo-controlled, US clinical trials were conducted in 1,036  
169 adolescent and adult patients ( $\geq 12$  years of age) with asthma to assess the efficacy and safety of  
170 fluticasone propionate inhalation powder in the treatment of asthma. Fixed dosages of 100, 250,  
171 and 500 mcg twice daily were compared with placebo to provide information about appropriate  
172 dosing to cover a range of asthma severity. Patients in these studies included those not  
173 adequately controlled with bronchodilators alone and those already maintained on daily inhaled  
174 corticosteroids. All doses were delivered by inhalation of the contents of 1 or 2 blisters from the  
175 DISKUS twice daily.

176 Figures 1 through 4 display results of pulmonary function tests (mean percent change from  
177 baseline in FEV<sub>1</sub> prior to AM dose) for 3 recommended dosages of fluticasone propionate  
178 inhalation powder (100, 250, and 500 mcg twice daily) and placebo from the four 12-week trials  
179 in adolescents and adults. These trials used predetermined criteria for lack of efficacy (indicators  
180 of worsening asthma), resulting in withdrawal of more patients in the placebo group. Therefore,  
181 pulmonary function results at Endpoint (the last evaluable FEV<sub>1</sub> result, including most patients'  
182 lung function data) are also displayed. Pulmonary function at recommended dosages of  
183 fluticasone propionate improved significantly compared with placebo by the first week of  
184 treatment, and improvement was maintained for up to 1 year or more.

185

186 **Figure 1. A 12-Week Clinical Trial Evaluating FLOVENT DISKUS**  
 187 **100 mcg Twice Daily in Adolescents and Adults Receiving**  
 188 **Bronchodilators Alone**

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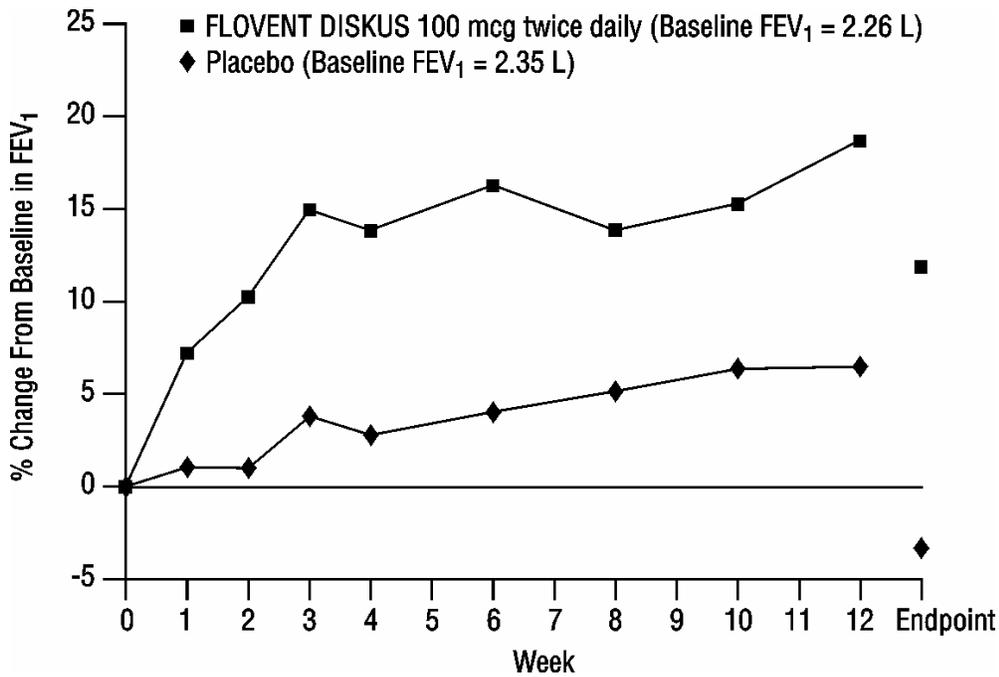


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192 **Figure 2. A 12-Week Clinical Trial Evaluating FLOVENT DISKUS**  
 193 **100 mcg Twice Daily in Adolescents and Adults Receiving Inhaled**  
 194 **Corticosteroids**

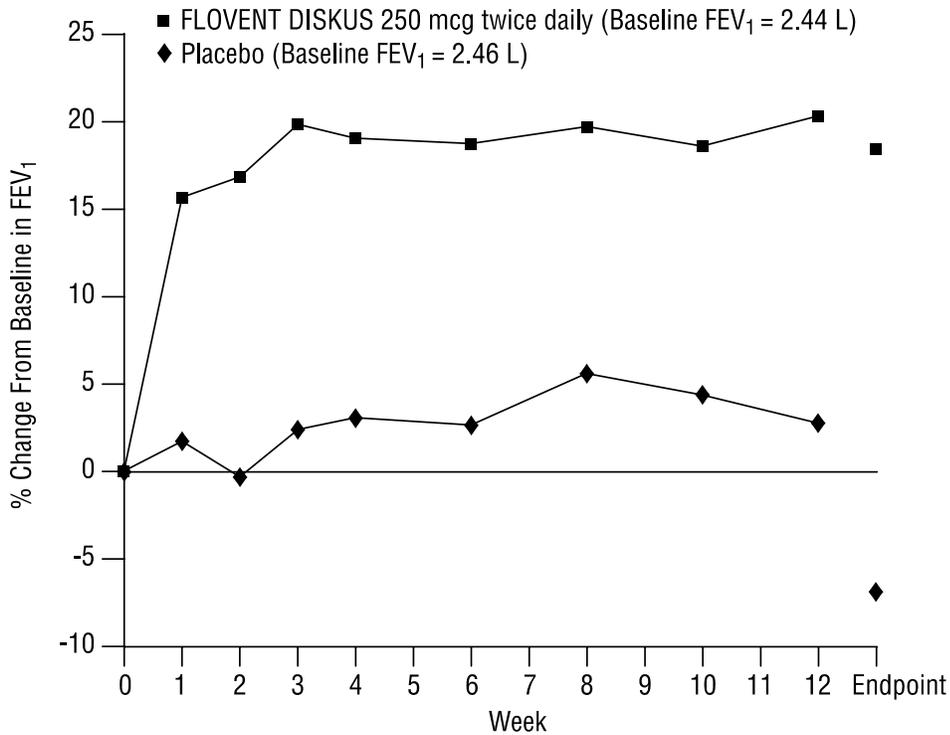
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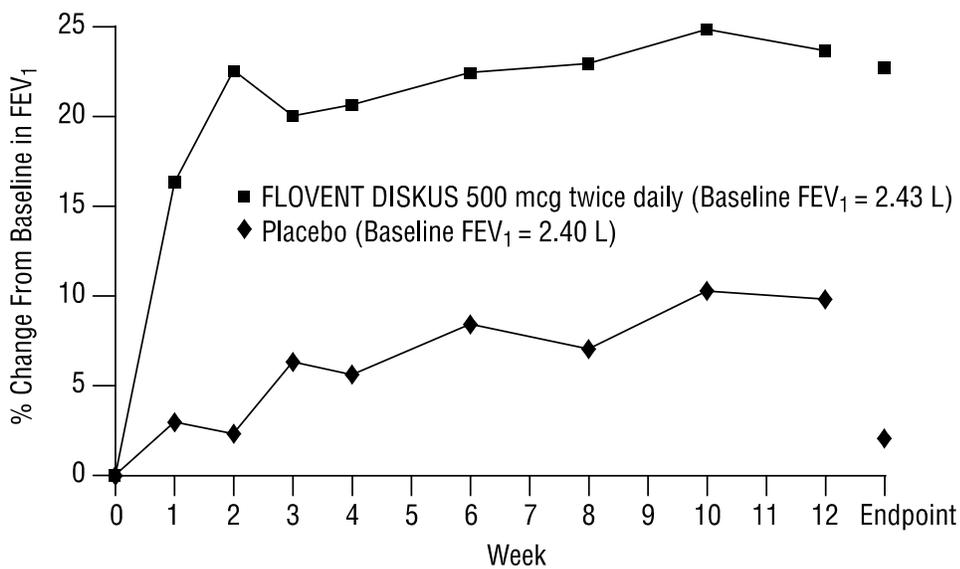
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198 **Figure 3. A 12-Week Clinical Trial Evaluating FLOVENT DISKUS**  
 199 **250 mcg Twice Daily in Adolescents and Adults Receiving Inhaled**  
 200 **Corticosteroids or Bronchodilators Alone**  
 201



202  
 203  
 204 **Figure 4. A 12-Week Clinical Trial Evaluating FLOVENT DISKUS**  
 205 **500 mcg Twice Daily in Adolescents and Adults Receiving Inhaled**  
 206 **Corticosteroids or Bronchodilators Alone**  
 207



208  
 209

210 | In all 4 efficacy trials, measures of pulmonary function (FEV<sub>1</sub>) ~~and AM PEF~~ were  
211 | statistically significantly improved as compared with placebo at all twice-daily doses. Patients  
212 | on all dosages of FLOVENT DISKUS were also ~~significantly~~ less likely to discontinue study  
213 | participation due to asthma deterioration (as defined by predetermined criteria for lack of  
214 | efficacy including lung function and patient-recorded variables such as AM PEF, albuterol use,  
215 | and nighttime awakenings due to asthma) compared with placebo.

216 | In a clinical trial of 111 patients with severe asthma requiring chronic oral prednisone therapy  
217 | (average baseline daily prednisone dose was 14 mg), fluticasone propionate given by inhalation  
218 | powder at doses of 500 and 1,000 mcg twice daily was evaluated. Both doses enabled a  
219 | statistically significantly larger percentage of patients to wean successfully from oral prednisone  
220 | as compared with placebo (75% of the patients on 500 mcg twice daily and 89% of the patients  
221 | on 1,000 mcg twice daily as compared with 9% of patients on placebo). Accompanying the  
222 | reduction in oral corticosteroid use, patients treated with fluticasone propionate had significantly  
223 | improved lung function and fewer asthma symptoms as compared with the placebo group.

224 | ***Pediatric Experience:*** A 12-week, placebo-controlled clinical trial was conducted in 437  
225 | patients (177 on fluticasone propionate via DISKUS) aged 4 to 11 years, approximately half of  
226 | whom were receiving inhaled corticosteroids at baseline. In this study, doses of fluticasone  
227 | propionate inhalation powder 50 and 100 mcg twice daily significantly improved FEV<sub>1</sub> (15%  
228 | and 18% change from baseline at Endpoint, respectively) compared to placebo (7% change).  
229 | Morning peak expiratory flow rate was also significantly improved with doses of fluticasone  
230 | propionate 50 and 100 mcg twice daily (26% and 27% change from baseline at Endpoint,  
231 | respectively) compared to placebo (14% change). In this study, patients on active treatment were  
232 | significantly less likely to discontinue treatment due to asthma deterioration (as defined by  
233 | predetermined criteria for lack of efficacy including lung function and patient recorded variables  
234 | such as AM PEFR, albuterol use, and nighttime awakenings due to asthma).

235 | Two other 12-week placebo-controlled clinical trials were conducted in 504 pediatric patients  
236 | with asthma, approximately half of whom were receiving inhaled corticosteroids at baseline. In  
237 | these studies, fluticasone propionate inhalation powder was efficacious at doses of 50 and  
238 | 100 mcg twice daily when compared to placebo on major endpoints including lung function and  
239 | symptom scores. Pulmonary function improved significantly compared with placebo by the first  
240 | week of treatment, and patients treated with fluticasone propionate were also less likely to  
241 | discontinue study participation due to asthma deterioration. One hundred ninety-two (192)  
242 | patients received fluticasone propionate for up to 1 year during an open-label extension. Data  
243 | from this open-label extension suggested that lung function improvements could be maintained  
244 | up to 1 year.

## 245 | **INDICATIONS AND USAGE**

246 | FLOVENT DISKUS is indicated for the maintenance treatment of asthma as prophylactic  
247 | therapy in adult and pediatric patients 4 years of age and older. It is also indicated for patients

248 requiring oral corticosteroid therapy for asthma. Many of these patients may be able to reduce or  
249 eliminate their requirement for oral corticosteroids over time.

250 FLOVENT DISKUS is NOT indicated for the relief of acute bronchospasm.

## 251 **CONTRAINDICATIONS**

252 FLOVENT DISKUS is contraindicated in the primary treatment of status asthmaticus or other  
253 acute episodes of asthma where intensive measures are required.

254 Hypersensitivity to any of the ingredients of these preparations contraindicates their use (see  
255 DESCRIPTION and ADVERSE REACTIONS: Observed During Clinical Practice: *Non-Site*  
256 *Specific*).

## 257 **WARNINGS**

258 Particular care is needed for patients who are transferred from systemically active  
259 corticosteroids to FLOVENT DISKUS because deaths due to adrenal insufficiency have  
260 occurred in patients with asthma during and after transfer from systemic corticosteroids to less  
261 systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a  
262 number of months are required for recovery of HPA function.

263 Patients who have been previously maintained on 20 mg or more per day of prednisone (or its  
264 equivalent) may be most susceptible, particularly when their systemic corticosteroids have been  
265 almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs  
266 and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection  
267 (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although  
268 fluticasone propionate inhalation powder may provide control of asthma symptoms during these  
269 episodes, in recommended doses it supplies less than normal physiological amounts of  
270 corticosteroid systemically and does NOT provide the mineralocorticoid activity that is  
271 necessary for coping with these emergencies.

272 During periods of stress or a severe asthma attack, patients who have been withdrawn from  
273 systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses)  
274 immediately and to contact their physicians for further instruction. These patients should also be  
275 instructed to carry a warning card indicating that they may need supplementary systemic  
276 corticosteroids during periods of stress or a severe asthma attack.

277 A drug interaction study in healthy subjects has shown that ritonavir (a highly potent  
278 cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate  
279 concentration, resulting in significantly reduced serum cortisol concentrations (see CLINICAL  
280 PHARMACOLOGY: Pharmacokinetics: *Drug Interactions* and PRECAUTIONS: Drug  
281 Interactions: *Inhibitors of Cytochrome P450*). During postmarketing use, there have been reports  
282 of clinically significant drug interactions in patients receiving fluticasone propionate and  
283 ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal  
284 suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not  
285 recommended unless the potential benefit to the patient outweighs the risk of systemic  
286 corticosteroid side effects.

287 Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid  
288 use after transferring to fluticasone propionate inhalation powder. In a clinical trial of 111  
289 patients, prednisone reduction was successfully accomplished by reducing the daily prednisone  
290 dose by 2.5 mg on a weekly basis during transfer to inhaled fluticasone propionate. Successive  
291 reduction of prednisone dose was allowed only when lung function; symptoms; and as-needed,  
292 short-acting beta-agonist use were better than or comparable to that seen before initiation of  
293 prednisone dose reduction. Lung function (FEV<sub>1</sub> or AM PEF), beta-agonist use, and asthma  
294 symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition  
295 to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms  
296 of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and  
297 hypotension.

298 Transfer of patients from systemic corticosteroid therapy to FLOVENT DISKUS may  
299 unmask conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis,  
300 conjunctivitis, eczema, arthritis, and eosinophilic conditions.

301 Persons who are using drugs that suppress the immune system are more susceptible to  
302 infections than healthy individuals. Chickenpox and measles, for example, can have a more  
303 serious or even fatal course in susceptible children or adults using corticosteroids. In such  
304 children or adults who have not had these diseases or been properly immunized, particular care  
305 should be taken to avoid exposure. How the dose, route, and duration of corticosteroid  
306 administration affect the risk of developing a disseminated infection is not known. The  
307 contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not  
308 known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG)  
309 may be indicated. If exposed to measles, prophylaxis with pooled intramuscular  
310 immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG  
311 and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be  
312 considered.

313 FLOVENT DISKUS is not to be regarded as a bronchodilator and is not indicated for rapid  
314 relief of bronchospasm.

315 As with other inhaled medications, bronchospasm may occur with an immediate increase in  
316 wheezing after dosing. If bronchospasm occurs following dosing with FLOVENT DISKUS, it  
317 should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with  
318 FLOVENT DISKUS should be discontinued and alternative therapy instituted.

319 Patients should be instructed to contact their physicians immediately when episodes of  
320 asthma that are not responsive to bronchodilators occur during the course of treatment with  
321 FLOVENT DISKUS. During such episodes, patients may require therapy with oral  
322 corticosteroids.

## 323 **PRECAUTIONS**

324 **General:** Orally inhaled corticosteroids may cause a reduction in growth velocity when  
325 administered to pediatric patients (see PRECAUTIONS: Pediatric Use.)

326 During withdrawal from systemically active corticosteroids, some patients may experience  
327 symptoms of corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and  
328 depression, despite maintenance or even improvement of respiratory function.

329 Fluticasone propionate will often help control asthma symptoms with less suppression of  
330 HPA function than therapeutically equivalent oral doses of prednisone. Since fluticasone  
331 propionate is absorbed into the circulation and can be systemically active at higher doses, the  
332 beneficial effects of FLOVENT DISKUS in minimizing HPA dysfunction may be expected only  
333 when recommended dosages are not exceeded and individual patients are titrated to the lowest  
334 effective dose. A relationship between plasma levels of fluticasone propionate and inhibitory  
335 effects on stimulated cortisol production has been shown after 4 weeks of treatment with  
336 fluticasone propionate. Since individual sensitivity to effects on cortisol production exists,  
337 physicians should consider this information when prescribing FLOVENT DISKUS.

338 Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated  
339 with FLOVENT DISKUS should be observed carefully for any evidence of systemic  
340 corticosteroid effects. Particular care should be taken in observing patients postoperatively or  
341 during periods of stress for evidence of inadequate adrenal response.

342 It is possible that systemic corticosteroid effects such as hypercorticism and adrenal  
343 suppression (including adrenal crisis) may appear in a small number of patients, particularly  
344 when FLOVENT DISKUS is administered at higher than recommended doses over prolonged  
345 periods of time. If such effects occur, the dosage of FLOVENT DISKUS should be reduced  
346 slowly, consistent with accepted procedures for reducing systemic corticosteroids and for  
347 management of asthma.

348 The long-term effects of fluticasone propionate in human subjects are not fully known. In  
349 particular, the effects resulting from chronic use of fluticasone propionate on developmental or  
350 immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients  
351 have received inhaled fluticasone propionate on a continuous basis for periods of 3 years or  
352 longer. In clinical studies with patients treated for 2 years with inhaled fluticasone propionate,  
353 no apparent differences in the type or severity of adverse reactions were observed after long-  
354 versus short-term treatment.

355 Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported  
356 in patients following the long-term administration of inhaled corticosteroids, including  
357 fluticasone propionate.

358 In clinical studies with inhaled fluticasone propionate, the development of localized  
359 infections of the pharynx with *Candida albicans* has occurred. When such an infection develops,  
360 it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while  
361 remaining on treatment with FLOVENT DISKUS, but at times therapy with FLOVENT  
362 DISKUS may need to be interrupted.

363 Inhaled corticosteroids should be used with caution, if at all, in patients with active or  
364 quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial,  
365 viral, or parasitic infections; or ocular herpes simplex.

366 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate may  
367 present with systemic eosinophilic conditions, with some patients presenting with clinical  
368 features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated  
369 with systemic corticosteroid therapy. These events usually, but not always, have been associated  
370 with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of  
371 fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with  
372 other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia,  
373 vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy  
374 presenting in their patients. A causal relationship between fluticasone propionate and these  
375 underlying conditions has not been established (see ADVERSE REACTIONS: Observed During  
376 Clinical Practice: *Eosinophilic Conditions*).

377 **Information for Patients:** Patients being treated with FLOVENT DISKUS should receive the  
378 following information and instructions. This information is intended to aid them in the safe and  
379 effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

380 It is important that patients understand how to use the DISKUS inhalation device  
381 appropriately and how it should be used in relation to other asthma medications they are taking.  
382 Patients should be given the following information:

- 383 1. Patients should use FLOVENT DISKUS at regular intervals as directed. Individual patients  
384 will experience a variable time to onset and degree of symptom relief and the full benefit  
385 may not be achieved until treatment has been administered for 1 to 2 weeks or longer. The  
386 patient should not increase the prescribed dosage but should contact the physician if  
387 symptoms do not improve or if the condition worsens.
- 388 2. Most patients are able to taste or feel a dose delivered from FLOVENT DISKUS. However,  
389 whether or not patients are able to sense delivery of a dose, you should instruct them not to  
390 exceed the recommended dose. You should instruct them to contact you or the pharmacist if  
391 they have questions.
- 392 3. FLOVENT DISKUS should not be used with a spacer device.
- 393 4. Patients who are pregnant or nursing should contact their physicians about the use of  
394 FLOVENT DISKUS.
- 395 5. Effective and safe use of FLOVENT DISKUS includes an understanding of the way that it  
396 should be used:
  - 397 • Never exhale into the DISKUS.
  - 398 • Never attempt to take the DISKUS apart.
  - 399 • Always activate and use the DISKUS in a level, horizontal position.
  - 400 • After inhalation, rinse the mouth with water and spit out. Do not swallow.
  - 401 • Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
  - 402 • Always keep the DISKUS in a dry place.
  - 403 • Discard **6 weeks (50-mcg strength) or 2 months (100- and 250-mcg strengths)** after  
404 removal from the moisture-protective foil overwrap pouch or after all blisters have been  
405 used (when the dose indicator reads “0”), whichever comes first.

- 406 6. Patients should be warned to avoid exposure to chickenpox or measles and, if they are  
407 exposed, to consult their physicians without delay.
- 408 7. For the proper use of FLOVENT DISKUS and to attain maximum improvement, the patient  
409 should read and carefully follow the Patient's Instructions for Use leaflet accompanying the  
410 product.

411 **Drug Interactions: Inhibitors of Cytochrome P450:** Fluticasone propionate is a substrate  
412 of cytochrome P450 3A4. A drug interaction study with fluticasone propionate aqueous nasal  
413 spray in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4  
414 inhibitor) can significantly increase plasma fluticasone propionate concentration, resulting in  
415 significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY:  
416 Pharmacokinetics: *Drug Interactions*). During postmarketing use, there have been reports of  
417 clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir,  
418 resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression.  
419 Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless  
420 the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

421 In a placebo-controlled crossover study in 8 healthy volunteers, coadministration of a single  
422 dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of ketoconazole  
423 (200 mg) to steady state resulted in increased plasma fluticasone propionate concentrations, a  
424 reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. Caution should  
425 be exercised when FLOVENT DISKUS is coadministered with ketoconazole and other known  
426 potent cytochrome P450 3A4 inhibitors.

427 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Fluticasone propionate  
428 demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately  
429 2 times the maximum recommended daily inhalation dose in adults and approximately 10 times  
430 the maximum recommended daily inhalation dose in children on a mcg/m<sup>2</sup> basis) for 78 weeks or  
431 in rats at inhalation doses up to 57 mcg/kg (less than the maximum recommended daily  
432 inhalation dose in adults and approximately equal to the maximum recommended daily  
433 inhalation dose in children on a mcg/m<sup>2</sup> basis) for 104 weeks.

434 Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in  
435 vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in  
436 vitro or in the mouse micronucleus test.

437 No evidence of impairment of fertility was observed in reproductive studies conducted in  
438 male and female rats at subcutaneous doses up to 50 mcg/kg (less than the maximum  
439 recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis). Prostate weight was  
440 significantly reduced at a subcutaneous dose of 50 mcg/kg.

441 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. Subcutaneous studies in the  
442 mouse and rat at 45 and 100 mcg/kg, respectively (less than the maximum recommended daily  
443 inhalation dose in adults on a mcg/m<sup>2</sup> basis), revealed fetal toxicity characteristic of potent  
444 corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate,  
445 and retarded cranial ossification. No teratogenicity was seen in the rat at inhalation doses up to

446 68.7 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup>  
447 basis).

448 In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of  
449 4 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup>  
450 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg  
451 (approximately 3 times the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup>  
452 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this  
453 study, consistent with the established low bioavailability following oral administration (see  
454 CLINICAL PHARMACOLOGY: Pharmacokinetics: *Absorption*).

455 Fluticasone propionate crossed the placenta following administration of a subcutaneous dose  
456 of 100 mcg/kg to mice (less than the maximum recommended daily inhalation dose in adults on a  
457 mcg/m<sup>2</sup> basis), a subcutaneous or an oral dose of 100 mcg/kg to rats (less than the maximum  
458 recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis), and an oral dose of 300 mcg/kg  
459 to rabbits (approximately 3 times the maximum recommended daily inhalation dose in adults on  
460 a mcg/m<sup>2</sup> basis).

461 There are no adequate and well-controlled studies in pregnant women. FLOVENT DISKUS  
462 should be used during pregnancy only if the potential benefit justifies the potential risk to the  
463 fetus.

464 Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to  
465 physiologic, doses suggests that rodents are more prone to teratogenic effects from  
466 corticosteroids than humans. In addition, because there is a natural increase in corticosteroid  
467 production during pregnancy, most women will require a lower exogenous corticosteroid dose  
468 and many will not need corticosteroid treatment during pregnancy.

469 **Nursing Mothers:** It is not known whether fluticasone propionate is excreted in human breast  
470 milk. However, other corticosteroids have been detected in human milk. Subcutaneous  
471 administration to lactating rats of 10 mcg/kg of tritiated fluticasone propionate (less than the  
472 maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) resulted in  
473 measurable radioactivity in the milk. Since there are no data from controlled trials on the use of  
474 FLOVENT DISKUS by nursing mothers, a decision should be made whether to discontinue  
475 nursing or to discontinue FLOVENT DISKUS, taking into account the importance of FLOVENT  
476 DISKUS to the mother.

477 **Pediatric Use:** Orally inhaled corticosteroids may cause a reduction in growth velocity when  
478 administered to pediatric patients. A reduction of growth velocity in children or teenagers may  
479 occur as a result of poorly controlled asthma or from use of corticosteroids including inhaled  
480 corticosteroids. The effects of long-term treatment of children and adolescents with inhaled  
481 corticosteroids, including fluticasone propionate, on final adult height are not known.

482 Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in  
483 growth in pediatric patients. In these studies, the mean reduction in growth velocity was  
484 approximately 1 cm/year (range, 0.3 to 1.8 cm/year) and appears to depend upon dose and  
485 duration of exposure. This effect was observed in the absence of laboratory evidence of HPA

486 axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic  
487 corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis  
488 function. The long-term effects of this reduction in growth velocity associated with orally  
489 inhaled corticosteroids, including the impact on final adult height, are unknown. The potential  
490 for “catch-up” growth following discontinuation of treatment with orally inhaled corticosteroids  
491 has not been adequately studied. The effects on growth velocity of treatment with orally inhaled  
492 corticosteroids for over 1 year, including the impact on final adult height, are unknown. The  
493 growth of children and adolescents receiving orally inhaled corticosteroids, including  
494 FLOVENT DISKUS, should be monitored routinely (e.g., via stadiometry). The potential  
495 growth effects of prolonged treatment should be weighed against the clinical benefits obtained  
496 and the risks associated with alternative therapies. To minimize the systemic effects of orally  
497 inhaled corticosteroids, including FLOVENT DISKUS, each patient should be titrated to the  
498 lowest dose that effectively controls his/her symptoms.

499 A 52-week, placebo-controlled study to assess the potential growth effects of fluticasone  
500 propionate inhalation powder (FLOVENT<sup>®</sup> ROTADISK<sup>®</sup>) at 50 and 100 mcg twice daily was  
501 conducted in the US in 325 prepubescent children (244 males and 81 females) aged 4 to  
502 11 years. The mean growth velocities at 52 weeks observed in the intent-to-treat population were  
503 6.32 cm/year in the placebo group (n = 76), 6.07 cm/year in the 50-mcg group (n = 98), and  
504 5.66 cm/year in the 100-mcg group (n = 89). An imbalance in the proportion of children entering  
505 puberty between groups and a higher dropout rate in the placebo group due to poorly controlled  
506 asthma may be confounding factors in interpreting these data. A separate subset analysis of  
507 children who remained prepubertal during the study revealed growth rates at 52 weeks of  
508 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and  
509 5.67 cm/year in the 100-mcg group (n = 79). In children 8.5 years of age, the mean age of  
510 children in this study, the range for expected growth velocity is: boys – 3<sup>rd</sup>  
511 percentile = 3.8 cm/year, 50<sup>th</sup> percentile = 5.4 cm/year, and 97<sup>th</sup> percentile = 7.0 cm/year; girls –  
512 3<sup>rd</sup> percentile = 4.2 cm/year, 50<sup>th</sup> percentile = 5.7 cm/year, and 97<sup>th</sup> percentile = 7.3 cm/year.

513 The clinical significance of these growth data is not certain. Physicians should closely follow  
514 the growth of children and adolescents taking corticosteroids by any route, and weigh the  
515 benefits of corticosteroid therapy against the possibility of growth suppression if growth appears  
516 slowed. Patients should be maintained on the lowest dose of inhaled corticosteroid that  
517 effectively controls their asthma.

518 The safety and effectiveness of FLOVENT DISKUS in children below 4 years of age have  
519 not been established.

520 **Geriatric Use:** Safety data have been collected on 280 patients (FLOVENT DISKUS n = 83,  
521 FLOVENT ROTADISK n = 197) 65 years of age or older and 33 patients (FLOVENT DISKUS  
522 n = 14, FLOVENT ROTADISK n = 19) 75 years of age or older who have been treated with  
523 fluticasone propionate inhalation powder in US and non-US clinical trials. There were no  
524 differences in adverse reactions compared to those reported by younger patients. In addition,  
525 there were no apparent differences in efficacy between patients 65 years of age or older and

526 younger patients. Fifteen patients 65 years of age or older and 1 patient 75 years of age or older  
 527 were included in the efficacy evaluation of US clinical studies.

528 **ADVERSE REACTIONS**

529 The incidence of common adverse events in Table 1 is based upon 7 placebo-controlled US  
 530 clinical trials in which 1,176 pediatric, adolescent, and adult patients (466 females and 710  
 531 males) previously treated with as-needed bronchodilators and/or inhaled corticosteroids were  
 532 treated with FLOVENT DISKUS (doses of 50 to 500 mcg twice daily for up to 12 weeks) or  
 533 placebo.

534  
 535 **Table 1. Overall Adverse Events With >3% Incidence in US Controlled Clinical Trials**  
 536 **With FLOVENT DISKUS in Patients With Asthma Previously Receiving**  
 537 **Bronchodilators and/or Inhaled Corticosteroids**

| Adverse Event                        | Placebo<br>(n = 543)<br>% | FLOVENT<br>DISKUS<br>50 mcg<br>Twice<br>Daily<br>(n = 178)<br>% | FLOVENT<br>DISKUS<br>100 mcg<br>Twice<br>Daily<br>(n = 305)<br>% | FLOVENT<br>DISKUS<br>250 mcg<br>Twice<br>Daily<br>(n = 86)<br>% | FLOVENT<br>DISKUS<br>500 mcg<br>Twice<br>Daily<br>(n = 64)<br>% |
|--------------------------------------|---------------------------|---|--|---|---|
| Ear, nose, and throat                |                           |   |  |   |   |
| Upper respiratory tract infection    | 16                        | 20  | 18   | 21  | 14  |
| Throat irritation                    | 8                         | 13  | 13   | 3   | 22  |
| Sinusitis/sinus infection            | 6                         | 9   | 10   | 6   | 6   |
| Upper respiratory inflammation       | 3                         | 5   | 5  | 0   | 5   |
| Rhinitis                             | 2                         | 4   | 3  | 1   | 2   |
| Oral candidiasis                     | 7                         | <1  | 9  | 6   | 5   |
| Gastrointestinal                     |                           |   |  |   |   |
| Nausea and vomiting                  | 4                         | 8   | 4  | 1   | 2   |
| Gastrointestinal discomfort and pain | 3                         | 4   | 3  | 2   | 2   |
| Viral gastrointestinal infection     | 1                         | 4   | 3  | 3   | 5   |
| Non-site specific                    |                           |   |  |   |   |
| Fever                                | 4                         | 7   | 7  | 1   | 2   |
| Viral infection                      | 2                         | 2   | 2  | 0   | 5   |
| Lower respiratory                    |                           |   |  |   |   |
| Viral respiratory infection          | 4                         | 4   | 5  | 1   | 2   |

|                                     |    |    |    |    |    |
|-------------------------------------|----|----|----|----|----|
| Cough                               | 4  | 3  | 5  | 1  | 5  |
| Bronchitis                          | 1  | 2  | 3  | 0  | 8  |
| Neurological                        |    |    |    |    |    |
| Headache                            | 7  | 12 | 12 | 2  | 14 |
| Musculoskeletal and trauma          |    |    |    |    |    |
| Muscle injury                       | 1  | 2  | 0  | 1  | 5  |
| Musculoskeletal pain                | 2  | 4  | 3  | 2  | 5  |
| Injury                              | <1 | 2  | <1 | 0  | 5  |
| Average duration of exposure (days) | 56 | 76 | 73 | 79 | 78 |

538

539 Table 1 includes all events (whether considered drug-related or nondrug-related by the  
540 investigator) that occurred at a rate of over 3% in any of the groups treated with FLOVENT  
541 DISKUS and were more common than in the placebo group. In considering these data,  
542 differences in average duration of exposure should be taken into account.

543 These adverse events were mostly mild to moderate in severity, with <2% of patients  
544 discontinuing the studies because of adverse events. Rare cases of immediate and delayed  
545 hypersensitivity reactions, including rash and other rare events of angioedema and  
546 bronchospasm, have been reported.

547 Other adverse events that occurred in the groups receiving FLOVENT DISKUS in these  
548 studies with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo  
549 were:

550 **Cardiovascular:** Palpitations.

551 **Drug Interaction, Overdose, and Trauma:** Soft tissue injuries, contusions and  
552 hematomas, wounds and lacerations, postoperative complications, burns, poisoning and toxicity,  
553 pressure-induced disorders.

554 **Ear, Nose, and Throat:** Ear signs and symptoms; rhinorrhea/postnasal drip;  
555 hoarseness/dysphonia; epistaxis; tonsillitis; nasal signs and symptoms; laryngitis; unspecified  
556 oropharyngeal plaques; otitis; ear, nose, throat, and tonsil signs and symptoms; ear, nose, and  
557 throat polyps; allergic ear, nose, and throat disorders; throat constriction.

558 **Endocrine and Metabolic:** Fluid disturbances, weight gain, goiter, disorders of uric acid  
559 metabolism, appetite disturbances.

560 **Eye:** Keratitis and conjunctivitis, blepharoconjunctivitis.

561 **Gastrointestinal:** Diarrhea, gastrointestinal signs and symptoms, oral ulcerations, dental  
562 discomfort and pain, gastroenteritis, gastrointestinal infections, abdominal discomfort and pain,  
563 oral erythema and rashes, mouth and tongue disorders, oral discomfort and pain, tooth decay.

564 **Hepatobiliary Tract and Pancreas:** Cholecystitis.

565 **Lower Respiratory:** Lower respiratory infections.

566 **Musculoskeletal:** Muscle pain, arthralgia and articular rheumatism, muscle cramps and  
567 spasms, musculoskeletal inflammation.

568 **Neurological:** Dizziness, sleep disorders, migraines, paralysis of cranial nerves.  
569 **Non-Site Specific:** Chest symptoms; malaise and fatigue; pain; edema and swelling;  
570 bacterial infections; fungal infections; mobility disorders; cysts, lumps, and masses.  
571 **Psychiatry:** Mood disorders.  
572 **Reproduction:** Bacterial reproductive infections.  
573 **Skin:** Skin rashes, urticaria, photodermatitis, dermatitis and dermatosis, viral skin infections,  
574 eczema, fungal skin infections, pruritus, acne and folliculitis.  
575 **Urology:** Urinary infections.  
576 Three (3) of the 7 placebo-controlled US clinical trials were pediatric studies. A total of 592  
577 patients 4 to 11 years were treated with FLOVENT DISKUS (doses of 50 or 100 mcg twice  
578 daily) or placebo; an additional 174 patients 4 to 11 years received FLOVENT ROTADISK at  
579 the same doses. There were no clinically relevant differences in the pattern or severity of adverse  
580 events in children compared with those reported in adults.  
581 In the first 16 weeks of a 52-week clinical trial in adult patients with asthma who previously  
582 required oral corticosteroids (daily doses of 5 to 40 mg oral prednisone), the effects of  
583 FLOVENT DISKUS 500 mcg twice daily (n = 41) and 1,000 mcg twice daily (n = 36) were  
584 compared with placebo (n = 34) for the frequency of reported adverse events. Adverse events,  
585 whether or not considered drug related by the investigators, reported in more than 5 patients in  
586 the group taking FLOVENT DISKUS and that occurred more frequently with FLOVENT  
587 DISKUS than with placebo are shown below (percent FLOVENT DISKUS and percent  
588 placebo). In considering these data, the increased average duration of exposure for patients  
589 taking FLOVENT DISKUS (105 days for FLOVENT DISKUS versus 75 days for placebo)  
590 should be taken into account.  
591 **Ear, Nose, and Throat:** Hoarseness/dysphonia (9% and 0%), nasal congestion/blockage  
592 (16% and 0%), oral candidiasis (31% and 21%), rhinitis (13% and 9%), sinusitis/sinus infection  
593 (33% and 12%), throat irritation (10% and 9%), and upper respiratory tract infection (31% and  
594 24%).  
595 **Gastrointestinal:** Nausea and vomiting (9% and 0%).  
596 **Lower Respiratory:** Cough (9% and 3%) and viral respiratory infections (9% and 6%).  
597 **Musculoskeletal:** Arthralgia and articular rheumatism (17% and 3%) and muscle pain  
598 (12% and 0%).  
599 **Non-Site Specific:** Malaise and fatigue (16% and 9%) and pain (10% and 3%).  
600 **Skin:** Pruritus (6% and 0%) and skin rashes (8% and 3%).  
601 **Observed During Clinical Practice:** In addition to adverse events reported from clinical  
602 trials, the following events have been identified during postapproval use of fluticasone  
603 propionate in clinical practice. Because they are reported voluntarily from a population of  
604 unknown size, estimates of frequency cannot be made. These events have been chosen for  
605 inclusion due to either their seriousness, frequency of reporting, or causal connection to  
606 fluticasone propionate or a combination of these factors.  
607 **Ear, Nose, and Throat:** Aphonia, facial and oropharyngeal edema, and throat soreness.

608 **Endocrine and Metabolic:** Cushingoid features, growth velocity reduction in  
609 children/adolescents, hyperglycemia, and osteoporosis.  
610 **Eye:** Cataracts.  
611 **Psychiatry:** Agitation, aggression, anxiety, depression, and restlessness. Behavioral  
612 changes, including hyperactivity and irritability, have been reported very rarely and primarily in  
613 children.  
614 **Non-Site Specific:** Very rare anaphylactic reaction, very rare anaphylactic reaction in  
615 patients with severe milk protein allergy.  
616 **Respiratory:** Asthma exacerbation, bronchospasm, chest tightness, dyspnea, immediate  
617 bronchospasm, pneumonia, and wheeze.  
618 **Skin:** Contusions and ecchymoses.  
619 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate may  
620 present with systemic eosinophilic conditions, with some patients presenting with clinical  
621 features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated  
622 with systemic corticosteroid therapy. These events usually, but not always, have been associated  
623 with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of  
624 fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with  
625 other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia,  
626 vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy  
627 presenting in their patients. A causal relationship between fluticasone propionate and these  
628 underlying conditions has not been established (see PRECAUTIONS: Eosinophilic Conditions).

## 629 **OVERDOSAGE**

630 Chronic overdosage may result in signs/symptoms of hypercorticism (see PRECAUTIONS:  
631 General). Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone  
632 propionate inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate  
633 inhalation aerosol was well tolerated. Doses of 1,320 mcg administered to healthy human  
634 volunteers twice daily for 7 to 15 days were also well tolerated. Repeat oral doses up to 80 mg  
635 daily for 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for 42 days in  
636 patients were well tolerated. Adverse reactions were of mild or moderate severity, and  
637 incidences were similar in active and placebo treatment groups. The oral and subcutaneous  
638 median lethal doses in mice and rats were >1,000 mg/kg (>2,000 and >4,100 times, respectively,  
639 the maximum recommended daily inhalation dose in adults and >9,600 and >20,000 times,  
640 respectively, the maximum recommended daily inhalation dose in children on a mg/m<sup>2</sup> basis).

## 641 **DOSAGE AND ADMINISTRATION**

642 FLOVENT DISKUS should be administered by the orally inhaled route only in patients  
643 4 years of age and older. Individual patients will experience a variable time to onset and degree  
644 of symptom relief. Maximum benefit may not be achieved for 1 to 2 weeks or longer after  
645 starting treatment.

646 After asthma stability has been achieved, it is always desirable to titrate to the lowest  
 647 effective dosage to reduce the possibility of side effects. For patients who do not respond  
 648 adequately to the starting dosage after 2 weeks of therapy, higher dosages may provide  
 649 additional asthma control. The safety and efficacy of FLOVENT DISKUS when administered in  
 650 excess of recommended dosages have not been established.

651 The recommended starting dosage and the highest recommended dosage of FLOVENT  
 652 DISKUS, based on prior asthma therapy, are listed in Table 2.

653

654 **Table 2. Recommended Dosages of FLOVENT DISKUS\***

655 **NOTE: In all patients, it is desirable to titrate to the lowest effective dosage once**  
 656 **asthma stability is achieved.**

| Previous Therapy                  | Recommended Starting Dosage            | Highest Recommended Dosage |
|-----------------------------------|--|----------------------------|
| <b>Adults and Adolescents</b>     |  |                            |
| Bronchodilators alone             | 100 mcg twice daily                    | 500 mcg twice daily        |
| Inhaled corticosteroids           | 100-250 mcg twice daily                | 500 mcg twice daily        |
| Oral corticosteroids <sup>†</sup> | 500-1,000 mcg twice daily <sup>‡</sup> | 1,000 mcg twice daily      |
| <b>Children 4 to 11 Years</b>     |  |                            |
| Bronchodilators alone             | 50 mcg twice daily                     | 100 mcg twice daily        |
| Inhaled corticosteroids           | 50 mcg twice daily                     | 100 mcg twice daily        |

657 \* Starting dosages above 100 mcg twice daily for adults and adolescents and 50 mcg twice  
 658 daily for children 4 to 11 years of age may be considered for patients with poorer asthma  
 659 control or those who have previously required doses of inhaled corticosteroids that are in  
 660 the higher range for that specific agent.

661 <sup>†</sup> **For Patients Currently Receiving Chronic Oral Corticosteroid Therapy:** Prednisone  
 662 should be reduced no faster than 2.5 mg/day on a weekly basis, beginning after at least  
 663 1 week of therapy with FLOVENT DISKUS. Patients should be carefully monitored for  
 664 signs of asthma instability, including serial objective measures of airflow, and for signs of  
 665 adrenal insufficiency (see WARNINGS). Once prednisone reduction is complete, the  
 666 dosage of fluticasone propionate should be reduced to the lowest effective dosage.

667 <sup>‡</sup> The choice of starting dosage should be made on the basis of individual patient  
 668 assessment. A controlled clinical study of 111 oral corticosteroid-dependent patients with  
 669 asthma showed few significant differences between the 2 doses of FLOVENT DISKUS on  
 670 safety and efficacy endpoints. However, inability to decrease the dose of oral  
 671 corticosteroids further during corticosteroid reduction may be indicative of the need to  
 672 increase the dose of fluticasone propionate up to the maximum of 1,000 mcg twice daily.

673

674 **Pediatric Use:** Because individual responses may vary, children previously maintained on  
 675 FLOVENT ROTADISK<sup>®</sup> 50 or 100 mcg twice daily may require dosage adjustments upon  
 676 transfer to FLOVENT DISKUS.

677 **Geriatric Use:** In studies where geriatric patients (65 years of age or older, see  
678 PRECAUTIONS: Geriatric Use) have been treated with fluticasone propionate inhalation  
679 powder, efficacy and safety did not differ from that in younger patients. Based on available data  
680 for FLOVENT DISKUS, no dosage adjustment is recommended.

681 **Directions for Use:** Illustrated Patient's Instructions for Use accompany each package of  
682 FLOVENT DISKUS.

### 683 HOW SUPPLIED

684 FLOVENT DISKUS 50 mcg is supplied as a disposable orange inhalation unit containing 60  
685 blisters. The drug product is packaged within an orange, plastic-coated, moisture-protective foil  
686 pouch (NDC 0173-0600-02). FLOVENT DISKUS 50 mcg is also supplied in an institutional  
687 pack of 1 disposable orange inhalation unit containing 28 blisters. The drug product is packaged  
688 within an orange, plastic-coated, moisture-protective foil pouch (NDC 0173-0600-00).

689 FLOVENT DISKUS 100 mcg is supplied as a disposable orange inhalation unit containing 60  
690 blisters. The drug product is packaged within an orange, plastic-coated, moisture-protective foil  
691 pouch (NDC 0173-0602-02). FLOVENT DISKUS 100 mcg is also supplied in an institutional  
692 pack of 1 disposable orange inhalation unit containing 28 blisters. The drug product is packaged  
693 within an orange, plastic-coated, moisture-protective foil pouch (NDC 0173-0602-00).

694 FLOVENT DISKUS 250 mcg is supplied as a disposable orange inhalation unit containing 60  
695 blisters. The drug product is packaged within an orange, plastic-coated, moisture-protective foil  
696 pouch (NDC 0173-0601-02). FLOVENT DISKUS 250 mcg is also supplied in an institutional  
697 pack of 1 disposable orange inhalation unit containing 28 blisters. The drug product is packaged  
698 within an orange, plastic-coated, moisture-protective foil pouch (NDC 0173-0601-00).

699 **Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F) in a dry place**  
700 **away from direct heat or sunlight. Keep out of reach of children. The DISKUS inhalation**  
701 **device is not reusable. The device should be discarded 6 weeks (50-mcg strength) or**  
702 **2 months (100- and 250-mcg strengths) after removal from the moisture-protective foil**  
703 **pouch or after all blisters have been used (when the dose indicator reads "0"), whichever**  
704 **comes first. Do not attempt to take the device apart.**

705  
706



707  
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709 Research Triangle Park, NC 27709

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